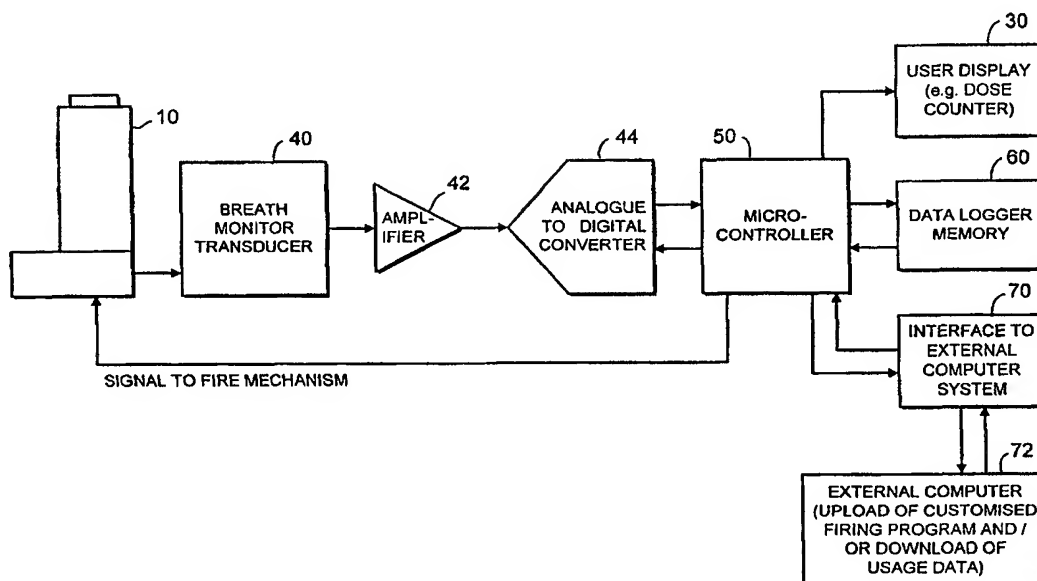




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(54) Title: MEDICAMENT DELIVERY SYSTEM



(57) Abstract

There is provided a system for the delivery of inhalable medicament comprising a monitor (40) for monitoring the breath cycle of a patient, a medicament container (2) having a release mechanism (4, 5) for releasing inhalable medicament therefrom, and an actuator (50) for actuating said release mechanism, the actuator (50) being actuable in response to a signal from the monitor (40). The monitor (40) provides the signal at a trigger point which is coupled to the end of the exhalation part of the breath cycle.

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Medicament delivery system

5 The present invention relates to a system for the delivery of inhalable medicament to a patient at a preset point in the breathing pattern of the patient. In particular, the invention relates to metered dose inhalers by means of which medicament may be delivered in metered doses.

10 It is well known to treat patients with medicaments contained in an aerosol, for example, in the treatment of respiratory disorders. It is also known to use for such treatment, medicaments which are contained in an aerosol and are administered to a patient by means of an inhalation device comprising a tubular housing or sleeve in which the aerosol container is located and an outlet tube leading out of the tubular housing. The aerosol containers used in such
15 inhalation devices are designed to deliver a predetermined dose of medicament upon each actuation by means of an outlet valve member at one end which can be opened either by depressing the valve member while the container is held stationary or by depressing the container while the valve member is held stationary. In the use of such devices, the aerosol container is placed in the
20 tubular housing with the outlet valve member of the container communicating via a support with the outlet tube, for example a nozzle or mouthpiece. When used for dispensing medicaments, for example in bronchodilation therapy, the patient then holds the housing in a more or less upright condition and the mouthpiece or nozzle of the inhalation device is placed in the mouth or nose of the patient. The
25 aerosol container is pressed towards the support to dispense a dose of medicament from the container which is then inhaled by the patient.

It may be understood that effective delivery of medicament to the patient using an inhalation device as described above is to an extent dependent on the
30 patient's ability to co-ordinate the actuation of the device (e.g. firing of the aerosol) with the taking of a sufficiently strong inward breath. For some patients the required co-ordination can present difficulties. Other patients, particularly those having severe respiratory problems, find it difficult to produce a reliable inward breath. Both of these sets of patients run the risk that they do not receive
35 the appropriate dose of medicament.

Breath-actuable or breath-assisted inhalation devices have been developed to address the needs of patients having poor co-ordination skills and/or unreliable breath capability. Such devices typically have a breath trigger mechanism which triggers release of medicament in response to the inward breath of a patient.

One problem inherent with such breath-triggered devices is that a certain amount of the inward breath is used up before the trigger is activated. The full inward breath is thus, not available for inhalation of medicament. Further, that initial part of the inward breath which is 'lost' prior to release of the medicament is a relatively strong and inhalation-effective portion of the full inward breath. Where the patient has poor breath capacity the loss of this portion of the inward breath may significantly compromise the amount of medicament which is deliverable to the lungs.

Another problem with such breath-triggered devices is that the medicament may not be released at the optimum point in the breath cycle.

The Applicants have now found that enhanced delivery of medicament is achievable by use of a system in which the breathing pattern of a patient is monitored and drug release is co-ordinated with a preset point in the breathing pattern. This preset point is selected to optimise the delivery of drug to the lung. It has been found to be particularly advantageous if the preset point is defined relative to, or indeed to coincide with, the end of the exhalation part of the breath cycle.

The Applicants have also now appreciated that at the end of the exhalation part of the breath cycle, the patient's mouth cavity is typically at rest which allows it to act as a natural 'spacer' element, thereby assisting with dispersal of the delivered medicament. There is thus, potentially less need for the use of a separate mechanical spacer element as is commonly used in conjunction with the mouthpiece of conventional inhalation devices.

According to one aspect of the present invention there is provided a system for the delivery of inhalable medicament comprising a monitor for monitoring the

breath cycle of a patient; a medicament container having a release mechanism for releasing inhalable medicament therefrom; and an actuator for actuating said release mechanism, said actuator being actuatable in response to a signal from said monitor. The monitor provides said signal at a trigger point which is coupled to the end of the exhalation part of the breath cycle.

By release mechanism herein it is meant any mechanism which enables release of medicament from the container. The release may be active in the sense that medicament is actively dispensed from the container (e.g. by the propellant-driven firing from an MDI aerosol container) or the release may be passive in the sense that medicament is merely made available for release (e.g. by removing a cover from a dry powder container) when the release mechanism is actuated.

By monitor herein it is meant any suitable means for monitoring, measuring, tracking or indicating the breath cycle of a patient including monitors employing one or more sensors. Suitable sensors include mechanical sensors such as those employing vanes or sails which are movable in response to airflow.

Preferably, the monitor comprises one or more sensors for sensing the pressure profile associated with the breath cycle. Pressure transducers are suitable sensors of this type.

Preferably, the monitor comprises one or more sensors for sensing the airflow profile associated with the breath cycle. Sprung vane sensors and sensors including anemometers are suitable sensors of this type.

Preferably, the monitor comprises one or more sensors for sensing the temperature profile associated with the breath cycle. The temperature of the inhaled and exhaled part of the breath cycle varies and may, thus, be used as a measurement tool.

Preferably, the monitor comprises one or more sensors for sensing the moisture profile associated with the breath cycle. The moisture content of the inhaled and exhaled part of the breath cycle varies and this also may be used as a measurement tool.

5 Preferably, the monitor comprises one or more sensors for sensing the chemical profile, particularly the oxygen or carbon dioxide profile, associated with the breath cycle. The chemical profile of the inhaled and exhaled part of the breath cycle varies and this further may be used as a measurement tool.

Preferably, the trigger point corresponds to the point at which the lungs of the patient are most empty.

10 Preferably, the monitor is connectable to an electronic information processor. The connection may be direct or via any suitable mechanical or electronic transfer means.

15 Preferably, the electronic information processor includes an active memory for storing information about the breath cycle.

Suitably, the electronic information processor includes a predictive algorithm or look-up table for predicting the optimum trigger point. For example, a real-time analysis of the patient waveform may be made and the optimum trigger point
20 derived by reference to that analysed waveform.

Suitably, the electronic information processor includes a second predictive algorithm or look-up table for predicting the optimum amount of medicament to release. Suitably, the electronic information processor includes a dose memory
25 for storing information about earlier delivered doses and reference is made to the dose memory in predicting the optimum amount of medicament to release.

Suitably, the system additionally comprises a display for displaying information about the optimum amount of medicament to release.
30

Suitably, the system additionally comprises a selector for selecting the amount of medicament to release.

In one aspect, the selector is manually operable.
35

In another aspect, the selector is automatically operable in response to a signal from the electronic information processor.

Suitably, the selector comprises a timing mechanism for varying the time interval of actuation of the actuator.

Suitably, the selector comprises a metering mechanism between the container and the release mechanism for metering a variable quantity of medicament for release.

Suitably, the selector comprises a multiple-fire mechanism for multiple actuation of the actuator, wherein each actuation releases a portion of the optimum amount of medicament. Successive actuations may be pulsed, for example such that the time intervals between actuations may be based on arithmetic or geometric progressions.

In one preferred aspect, the medicament container is an aerosol container and said release mechanism is an aerosol valve. Preferably, the aerosol valve includes a metering chamber for metering the release of medicament. More preferably, the metering chamber is of variable volume. The volume of the metering chamber may be for example, be varied to provide the optimum amount of medicament for release. In one preferred aspect, the volume of the metering chamber is variable automatically in response to a dosing signal sent from the electronic information processor.

Various types of variable volume metering chambers are envisaged. Suitable chambers comprise a fixed volume chamber whose metering volume is variable by insertion of a plunger or piston. The piston or plunger may have a fixed form or alternatively may comprises an element of variable shape and volume such as an inflatable balloon. Other suitable chambers comprise a chamber which is expandable because it is formed from a flexible/expandable material. Further suitable chambers have telescopic or concertina arrangements to allow for mechanical expansion of the metering volume.

In another preferred aspect, the medicament container is a dry-powder container or a liquid container, that is to say a container respectively suitable for containing medicament in dry-powder or liquid form.

5 Preferably, the actuator comprises an energy store for storing energy which energy is releasable to activate the release mechanism of the medicament container. The energy store comprises in preferred aspects, a biasable resilient member such as a spring, a source of compressed fluid such as a canister of compressed gas (e.g. carbon dioxide or air), or a voltaic cell or battery of voltaic
10 cells. Chemical energy sources are also suitable and might include chemical propellant or ignition mixtures. Other sources might include physical explosives such as liquefied or solidified gas in a canister which burst when heated or exposed to the atmosphere.

15 Preferably, the system additionally comprises a safety mechanism to prevent unintended multiple actuations of the actuator. The patient is thereby protected from inadvertently receiving multiple doses of medicament in a situation where they take a number of short rapid breaths. More preferably, the safety mechanism imposes a time delay between successive actuations of the actuator.
20 The time delay is typically of the order of from three to thirty seconds.

An actuation counter which can be mechanical or electronic may be provided to the system.

25 A medicament release counter, such as a dose counter, may be provided to the system. This may be mechanical or electronic. The counter may be coupled to a visual display to provide feedback to the patient as to amount of drug released or remaining in the container.

30 A manual override can be provided to the system for use in the event of emergency or system failure.

According to another aspect of the present invention there is provided an inhalation device for the delivery of inhalable medicament comprising a housing
35 and a system as described above. Suitable housings typically comprise a cavity

for receipt of the medicament container and an opening in the form of a mouthpiece or nozzle through which the medicament is delivered to the patient.

According to a further aspect of the present invention there is provided a method
5 for the delivery of inhalable medicament to a patient comprising

(i) monitoring the breath cycle of a patient by use of a monitor;

10 (ii) at a trigger point, sending an actuation signal from said monitor to an actuator;

(iii) on receipt of said actuation signal by said actuator, actuating the release of inhalable medicament to the patient,

15 The trigger point is coupled to the end of the exhalation part of the breath cycle.

In step (i) a real-time analysis of the patient waveform may be made and comparison made with a medically acceptable waveform. Steps (i) to (iii) can then repeated until the patient waveform sufficiently matches the medically
20 acceptable waveform.

Preferably, the method comprises

25 (i) monitoring a plurality of breath cycles of a patient by use of a monitor;

(ii) analysing said plurality of breath cycles to define an averaged breath cycle for the patient;

30 (iii) predicting a trigger point from said averaged breath cycle, the trigger point being coupled to the end of the exhalation part of the averaged breath cycle;

(iv) monitoring a further breath cycle and at said predicted trigger point sending an actuation signal from said monitor to an actuator;

(v) on receipt of said actuation signal by said actuator, actuating the release of inhalable medicament to the patient.

A system according to the invention will now be described with reference to the accompanying drawings in which:

Figure 1. is a sectional view of a standard metered dose inhaler;

Figure 2. is a perspective view of an inhalation device in accord with the present invention;

Figure 3. is a graphical representation of a patient breathing pattern;

Figure 4. is a schematic representation of a system in accord with the present invention; and

Figure 5. is a flow-chart indicating the operation of a system in accord with the present invention.

The standard metered dose inhaler shown in Fig 1 comprises a tubular housing 1 in which an aerosol container 2 can be located. The housing is open at one end (which will hereinafter be considered to be the top of the device for convenience of description) and is closed at the other. An outlet 3 leads laterally from the closed end of the housing 1. In the embodiment illustrated, the outlet 3 is in the form of a mouthpiece intended for insertion into the mouth of the patient but it may, if desired, be designed as a nozzle for insertion into the patient's nostril.

The aerosol container 2 has an outlet valve stem 4 at one end. This valve member can be depressed to release a measured dose from the aerosol container or, alternatively, the valve stem 4 can be fixed and the main body of the container can be moved relative to the valve member to release the dose.

As shown clearly in Fig 1, the aerosol container 2 is located in the housing 1 so that one end protrudes from its open top. Spacer ribs (not shown) may be

provided inside the housing to hold the external surface of the container 2 spaced from the internal surface of the housing 1. A support 5 is provided at the lower end of the housing 1 and has a passage 6 in which the valve stem 4 of the aerosol container 2 can be located and supported. A second passage 7 is provided in the support 5 and is directed towards the interior of the outlet 3.

Thus, when the parts are in the positions shown in Fig 1, the protruding portion of the aerosol container 2 can be depressed to move the container relative to the valve stem 4 to open the valve and a dose of medicament contained in the aerosol will be discharged through the passage 7 and into the outlet 3 from which it can be inhaled by a patient. One dose will be released from the aerosol container each time it is fully depressed.

Figure 2. shows a metered dose inhaler of the general type illustrated in Figure 1. which includes an electronic device for monitoring the breath cycle of a patient. The device comprises housing 10 within which an electronic information processor 20 is housed. The electronic information processor 20 is connected to a sensor (not visible) for sensing the breathing pattern of the patient and an actuator (not visible) for actuating the release of aerosol from the container 2.

Visual display monitor 30 allows for display of information relating to doses dispensed from the container 2.

Figure 3. depicts the breathing pattern of a patient in simplified graphical form wherein the vertical axis represents the volume of air in the lungs and the horizontal axis represents time. A trigger zone 40 is indicated which corresponds to the portion in the breath cycle at which the lungs are at their most empty.

Figure 4. is a block diagram illustrating a system herein. Inhaler 10 includes breath monitor transducer 40 for sensing the pressure or flow profile through the device, thereby enabling the breathing pattern of a patient to be monitored. The breath monitor transducer 40 connects via amplifier 42 and analogue to digital converter 44 to micro-controller 50. The micro-controller 50 is for example, contained within a device attached to the inhaler 10 (as in Figure 2.). The micro-controller 50 is in communication with a user display 30 for the visual display of

information e.g. relating to number of doses dispensed. The micro-controller 50 is also in communication with a memory 60 for storage of information relating to the breathing pattern of the patient. The micro-controller 50 further communicates with an interface 70 to an external computer system 72. The
5 external computer system 72 allows for the use of customised software such as that enabling visual display of the breathing pattern of the patient. Importantly, the micro-controller 50 also communicates with an actuator on the inhaler 10, thereby enabling an actuation signal to be sent at the appropriate trigger point.

10 Figure 5. is a flow diagram illustrating a method of use of a system in accord with the invention. At point 80 the equipment is powered up, typically from a low energy 'sleep' mode. Readings from the breath monitor transducer are then taken at point 82. These readings are analysed at point 83 and corrections made for any artefacts such as if the patient coughs or takes short, sudden breaths. A
15 picture of the patient's breathing pattern is, thus, assembled. At point 84 an assessment is made as to whether the patient is at the end of the exhalation part of the breath cycle. The trigger point is at the end of breath point, or at a point coupled thereto. At point 85 a calculation is made of the dose required. The calculation is based on trend data and on the current breathing pattern. At point
20 86 the dose is fired. A loop involving an optional programmable delay 87 may be included to allow for the delivery of dose by multiple, rapid firing of partial doses. At point 88 a check is made if the patient requires further doses. If further doses are required, there is a loop back to point 82.

25 If no further doses are required, point 90 is reached at which a calculation is made of the total dose delivered in the most recent firing pattern and the dose display is updated. Data relating to the most recent dose delivery event is logged into a memory at point 92. A delay is triggered at point 94 to prevent reuse of the system within a set time period. This delay acts as a safety mechanism. At point
30 96, the system is reset to the powered down 'sleep' mode.

The system of the invention is suitable for dispensing medicament, particularly for the treatment of respiratory disorders such as disorders of the lungs and bronchial tracts including asthma and chronic obstructive pulmonary disorder
35 (COPD).

Appropriate medicaments may be selected from, for example, analgesics, e.g., codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, e.g., diltiazem; antiallergics, e.g., cromoglycate, ketotifen or nedocromil; antiinfectives e.g., cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, e.g., methapyrilene; anti-inflammatories, e.g., beclomethasone dipropionate, fluticasone propionate, flunisolide, budesonide, rofleponide, mometasone furoate or triamcinolone acetonide; antitussives, e.g., noscapine; bronchodilators, e.g., albuterol, salmeterol, ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimeterol, terbutaline, isoetharine, tulobuterol, or (-)-4-amino-3,5-dichloro- α -[[[6-[2-(2-pyridinyl)ethoxy] hexyl]methyl] benzenemethanol; diuretics, e.g., amiloride; anticholinergics, e.g., ipratropium, tiotropium, atropine or oxitropium; hormones, e.g., cortisone, hydrocortisone or prednisolone; xanthines, e.g., aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; therapeutic proteins and peptides, e.g., insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts, (e.g., as alkali metal or amine salts or as acid addition salts) or as esters (e.g., lower alkyl esters) or as solvates (e.g., hydrates) to optimise the activity and/or stability of the medicament.

Preferred medicaments are selected from albuterol, salmeterol, fluticasone propionate and beclomethasone dipropionate and salts or solvates thereof, e.g., the sulphate of albuterol and the xinafoate of salmeterol, and any mixtures thereof.

Medicaments can also be delivered in combinations. Preferred formulations containing combinations of active ingredients contain salbutamol (e.g., as the free base or the sulphate salt) or salmeterol (e.g., as the xinafoate salt) in combination with an antiinflammatory steroid such as a beclomethasone ester (e.g., the dipropionate) or a fluticasone ester (e.g., the propionate).

The medicaments can be in any suitable form. Preferred forms include aerosols comprising medicament suspended in a propellant with optionally one or more

solvents; dry powders comprising micronized medicament and optionally one or more excipients; and solutions including aqueous solutions.

5 It will be understood that the present disclosure is for the purpose of illustration only and the invention extends to modifications, variations and improvements thereto.

10 The application of which this description and claims form part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described therein. They may take the form of product, method or use claims and may include, by way of example and without limitation, one or more of the following claims:

CLAIMS:

1. A system for the delivery of inhalable medicament comprising
5 a monitor for monitoring the breath cycle of a patient;
a medicament container having a release mechanism for releasing inhalable medicament therefrom; and
10 an actuator for actuating said release mechanism, said actuator being actuable in response to a signal from said monitor,
characterized in that the monitor provides said signal at a trigger point which is coupled to the end of the exhalation part of the breath cycle.
15
2. A system according to claim 1, wherein said monitor comprises one or more sensors for sensing the pressure profile associated with the breath cycle.
3. A system according to either of claims 1 or 2, wherein said monitor
20 comprises one or more sensors for sensing the airflow profile associated with the breath cycle.
4. A system according to any of claims 1 to 3, wherein said monitor
25 comprises one or more sensors for sensing the temperature profile associated with the breath cycle.
5. A system according to any of claims 1 to 4, wherein said monitor
comprises one or more sensors for sensing the moisture profile associated with the breath cycle.
30
6. A system according to any of claims 1 to 5, wherein said monitor
comprises one or more sensors for sensing the oxygen or carbon dioxide profile associated with the breath cycle.

7. A system according to any of claims 1 to 6, wherein the trigger point corresponds to the point at which the lungs of the patient are most empty.
- 5 8. A system according to any of claims 1 to 7, wherein said monitor is connectable to an electronic information processor.
9. A system according to claim 8, wherein said electronic information processor includes an active memory for storing information about the breath cycle.
- 10 10. A system according to claim 9, wherein said electronic information processor includes a predictive algorithm for predicting the optimum trigger point.
- 15 11. A system according to claim 9, wherein said electronic information processor includes a look-up table for predicting the optimum trigger point.
12. A system according to any of claims 9 to 11, wherein said electronic information processor includes a second predictive algorithm for predicting the optimum amount of medicament to release.
- 20 13. A system according to any of claims 9 to 11, wherein said electronic information processor includes a second look-up table for predicting the optimum amount of medicament to release.
- 25 14. A system according to either of claim 12 or 13, wherein said electronic information processor includes a dose memory for storing information about earlier delivered doses and reference is made to the dose memory in predicting the optimum amount of medicament to release.
- 30 15. A system according to any of claims 12 to 14, additionally comprising a display for displaying information about the optimum amount of medicament to release.

16. A system according to any of claims 12 to 15, additionally comprising a selector for selecting the amount of medicament to release.

5 17. A system according to claim 16, wherein the selector is manually operable.

18. A system according to claim 16, wherein the selector is operable in response to a signal from the electronic information processor.

10 19. A system according to any of claims 16 to 18, wherein the selector comprises a timing mechanism for varying the time interval of actuation of the actuator.

15 20. A system according to any of claims 16 to 19, wherein the selector comprises a metering mechanism between the container and the release mechanism for metering a variable quantity of medicament for release.

20 21. A system according to any of claims 16 to 20, wherein the selector comprises a multiple-fire mechanism for multiple actuation of the actuator, wherein each actuation releases a portion of the optimum amount of medicament.

25 22. A system according to any of claims 1 to 21, wherein said medicament container is an aerosol container and said release mechanism is an aerosol valve.

23. A system according to claim 22, wherein said aerosol valve includes a metering chamber for metering the release of medicament.

30 24. A system according to claim 23, wherein the metering chamber has a variable metering volume.

35 25. A system according to claim 24, wherein the metering chamber comprises a chamber of fixed volume which metering volume is variable by insertion of a plunger or piston.

26. A system according to claim 24, wherein the metering chamber is formed from an expandable material.

27. A system according to claim 24, wherein the metering chamber has a telescopic or concertina arrangement.

28. A system according to any of claims 1 to 21, wherein said medicament container is a dry-powder container or a liquid container.

29. A system according to any of claims 1 to 28, wherein said actuator comprises an energy store for storing energy which energy is releasable to activate the release mechanism of the medicament container.

30. A system according to claim 29, wherein said energy store comprises a biasable resilient member.

31. A system according to claim 30, wherein said biasable resilient member is a spring.

32. A system according to claim 29, wherein said energy store comprises a source of compressed fluid, preferably compressed gas.

33. A system according to claim 29, wherein said energy store comprises a voltaic cell or battery of voltaic cells.

34. A system according to claim 29, wherein said energy store comprises a chemical energy source, preferably a chemical propellant or ignition mixture.

35. A system according to claim 29, wherein said energy store comprises a physically explosive energy source.

36. A system according to any of claims 1 to 35, additionally comprising a safety mechanism to prevent unintended multiple actuations of the actuator.

37. A system according to claim 36, wherein said safety mechanism imposes a time delay between successive actuations of the actuator.

5 38. A system according to any of claims 1 to 37, additionally comprising an actuation counter.

39. A system according to any of claims 1 to 38, additionally comprising a medicament release counter, preferably a dose counter.

10 40. A system according to any of claims 1 to 39, additionally comprising a manual override.

15 41. An inhalation device for the delivery of inhalable medicament comprising a housing and a system according to any of claims 1 to 40.

42. A method for the delivery of inhalable medicament to a patient comprising

20 (i) monitoring the breath cycle of a patient by use of a monitor;

(ii) at a trigger point, sending an actuation signal from said monitor to an actuator;

25 (iii) on receipt of said actuation signal by said actuator, actuating the release of inhalable medicament to the patient,

characterized in that said trigger point is coupled to the end of the exhalation part of the breath cycle.

30 43. Method according to claim 42, wherein steps (i) to (iii) are repeated until the breath cycle corresponds to a medically acceptable form.

44. Method according to claim 42, comprising

35 (i) monitoring a plurality of breath cycles of a patient by use of a monitor;

(ii) analysing said plurality of breath cycles to define an averaged breath cycle for the patient;

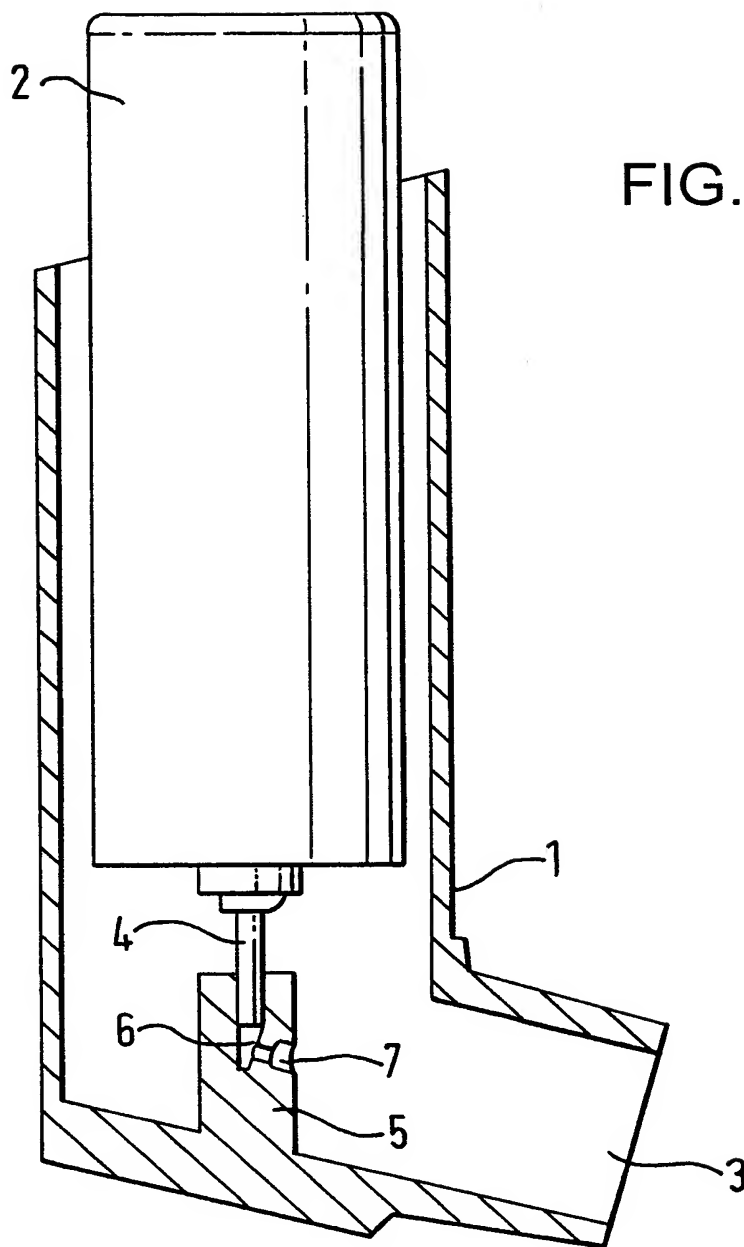
5 (iii) predicting a trigger point from said averaged breath cycle, the trigger point being coupled to the end of the exhalation part of the averaged breath cycle;

(iv) monitoring a further breath cycle and at said predicted trigger point sending an actuation signal from said monitor to an actuator;

10

(v) on receipt of said actuation signal by said actuator, actuating the release of inhalable medicament to the patient.

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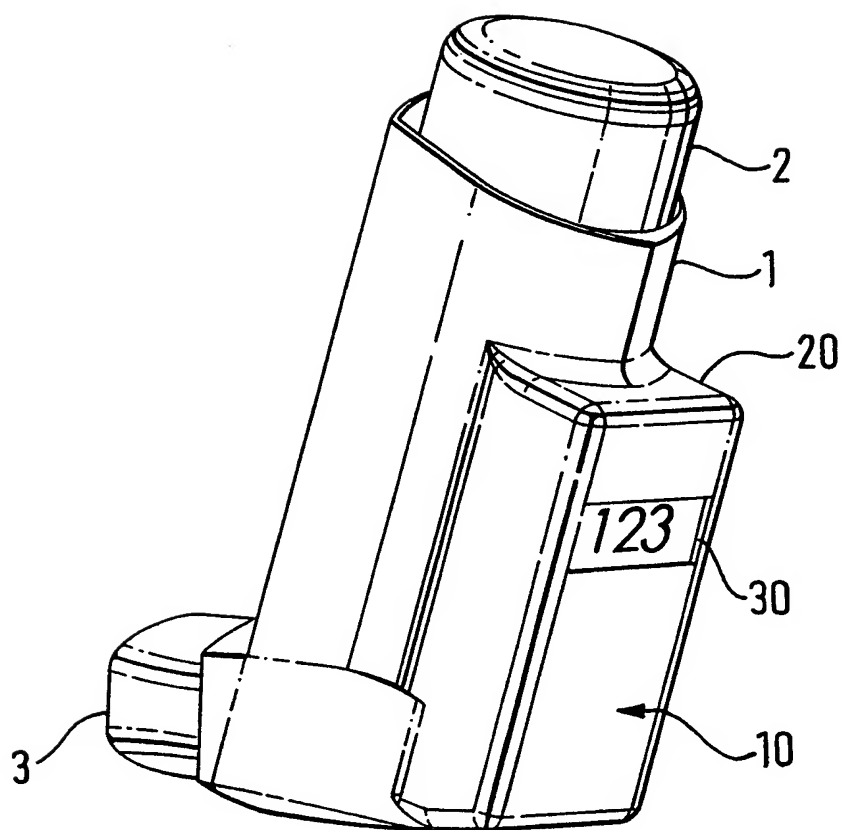


FIG. 2

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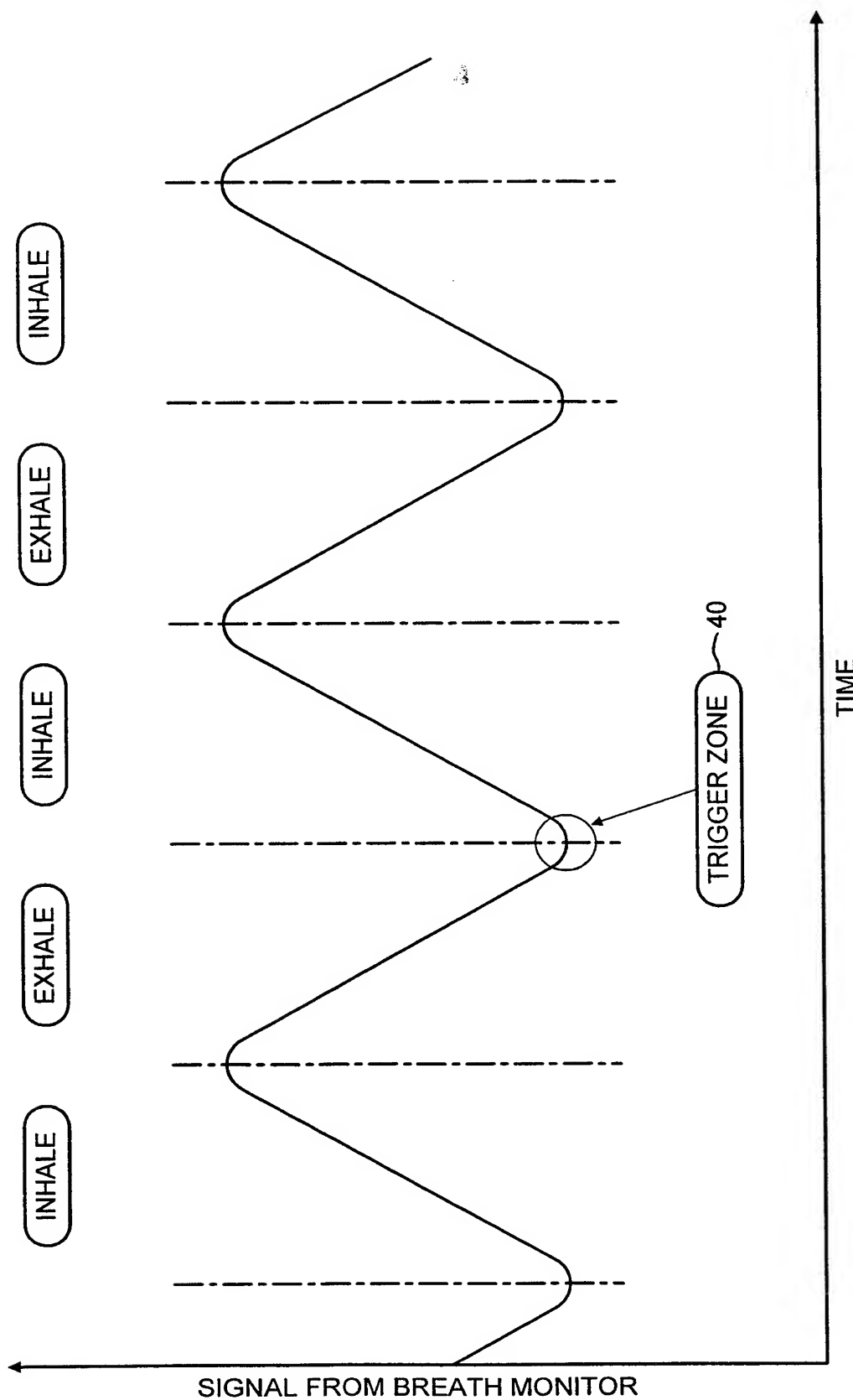


FIG. 3

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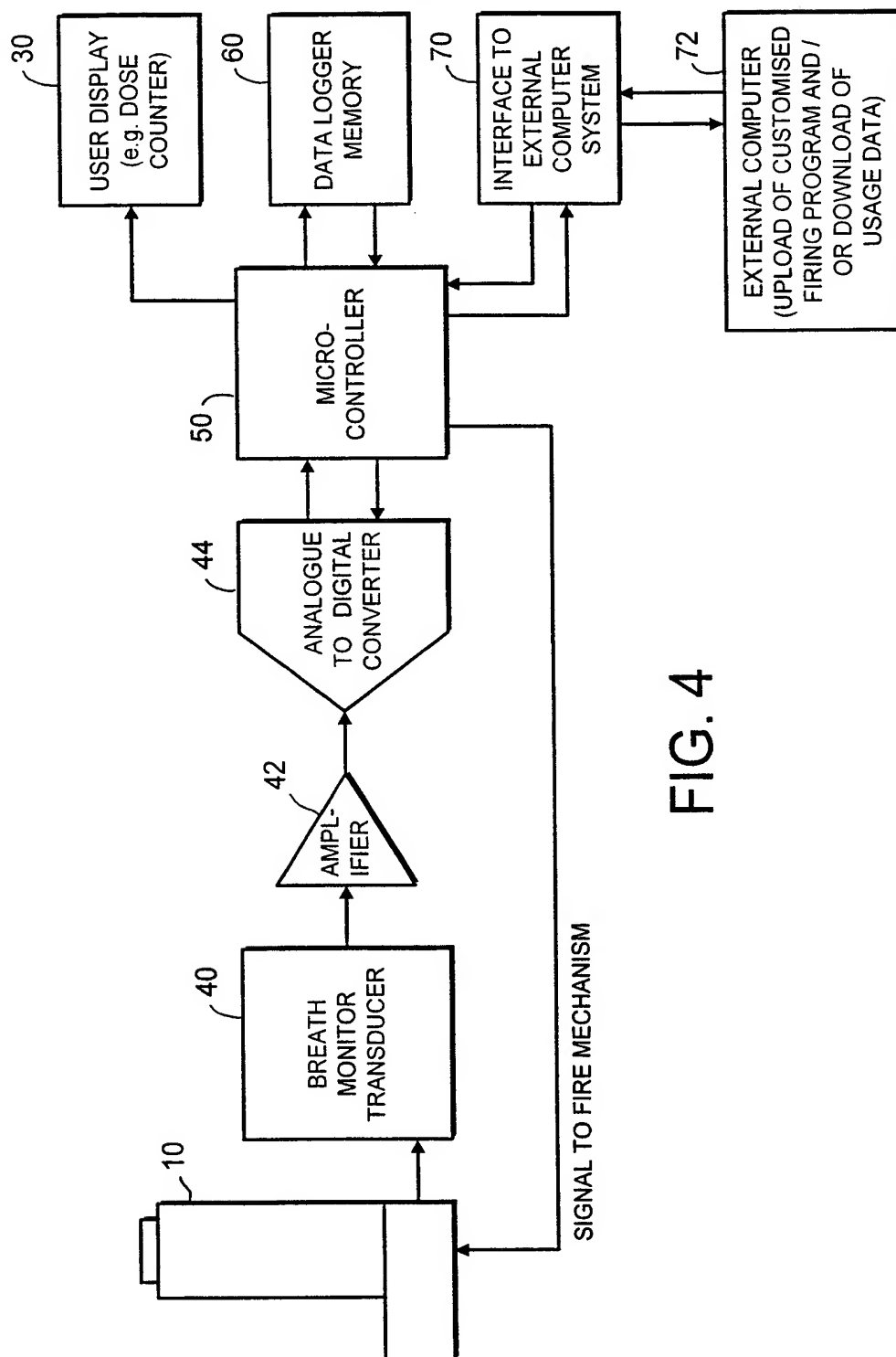


FIG. 4

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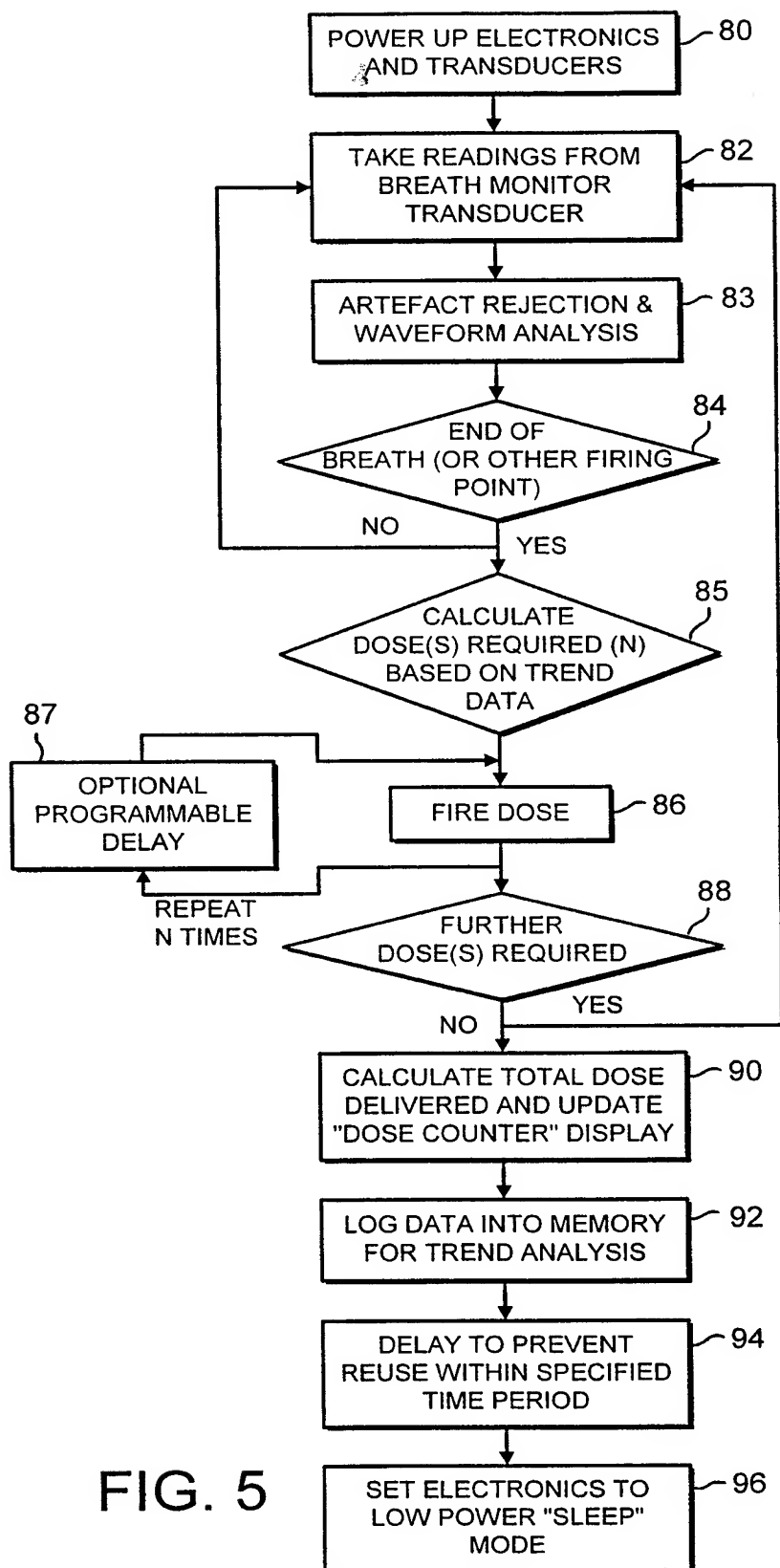


FIG. 5

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/01443

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M11/00 A61M15/00 A61M16/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 92 12750 A (VORTAN MEDICAL TECHNOLOGY INC) 6 August 1992 (1992-08-06)	1,2, 7-21,28, 32,38-41
	abstract	
	page 3, line 27 -page 4, line 30	
	page 9, line 25 -page 12, line 34	
	page 13, line 28-34	
Y	figures	3,4,22, 23, 29-31, 36,37
A		5,6, 24-27, 33-35

	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

1 August 2000

Date of mailing of the international search report

09.08.00

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Lager, J

INTERNATIONAL SEARCH REPORT

Inter. Appl. Application No
PCT/EP 00/01443

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y A	US 5 813 397 A (GOODMAN DAVID E ET AL) 29 September 1998 (1998-09-29) abstract column 1, line 17-21 column 4, line 65 -column 7, line 20 column 12, line 16-46 column 16, line 11-27 column 17, line 19-34 figures ---	3,22,23, 36,37 1,2, 4-21, 24-35
Y A	US 5 743 252 A (RUBSAMEN REID M ET AL) 28 April 1998 (1998-04-28) abstract column 4, line 15-45 column 6, line 30-50 column 7, line 1 -column 8, line 19 ---	4 1-3,5-41
Y A	US 5 520 166 A (RITSON CARL ET AL) 28 May 1996 (1996-05-28) abstract; figures 6-11 column 14, line 29-60 column 15, line 55 -column 18, line 3 ---	29-31 1-28, 32-41
A	US 5 608 647 A (RUBSAMEN REID M ET AL) 4 March 1997 (1997-03-04) abstract; figures column 3, line 49 -column 5, line 20 ---	1-41
A	US 5 469 750 A (LLOYD PETER M ET AL) 28 November 1995 (1995-11-28) abstract column 4, line 11-63 column 6, line 60 -column 8, line 18 ---	1-41
A	WO 99 04841 A (NORDMAN CATHERINE A ;SCHMIDT MATTHEW F (US); BUAN JOHN S (US); MIN) 4 February 1999 (1999-02-04) abstract ---	5,6
A	US 5 842 467 A (GRECO MICHAEL) 1 December 1998 (1998-12-01) figures ---	24,26
A	US 3 695 263 A (KIPLING BARRY JOHN) 3 October 1972 (1972-10-03) figures ---	25
A	US 4 176 663 A (HEWLETT ANTHONY M) 4 December 1979 (1979-12-04) figures -----	27

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/01443

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 42-44
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/01443

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9212750 A	06-08-1992	US 5322057 A AU 1342092 A CA 2099665 A EP 0568648 A JP 6505184 T	21-06-1994 27-08-1992 25-07-1992 10-11-1993 16-06-1994
US 5813397 A	29-09-1998	US 5655516 A US 5542410 A US 5404871 A US 5826570 A AT 188617 T CA 2082168 C DE 69230546 D DE 69230546 T EP 0529053 A ES 2141104 T JP 9164205 A JP 2613347 B US 5394866 A US 5469750 A US 5450336 A US 5392768 A WO 9215353 A US 5522378 A US 5622162 A US 5497764 A US 5520166 A US 5608647 A US 5743252 A US 5755218 A	12-08-1997 06-08-1996 11-04-1995 27-10-1998 15-01-2000 26-03-1996 17-02-2000 21-06-2000 03-03-1993 16-03-2000 24-06-1997 28-05-1997 07-03-1995 28-11-1995 12-09-1995 28-02-1995 17-09-1992 04-06-1996 22-04-1997 12-03-1996 28-05-1996 04-03-1997 28-04-1998 26-05-1998
US 5743252 A	28-04-1998	US 5608647 A US 5450336 A US 5404871 A AU 6130594 A EP 0683890 A JP 8509545 T WO 9417370 A AT 188617 T CA 2082168 C DE 69230546 D DE 69230546 T EP 0529053 A ES 2141104 T JP 9164205 A JP 2613347 B US 5394866 A US 5469750 A US 5392768 A WO 9215353 A US 5522378 A US 5542410 A US 5622162 A US 5497764 A US 5520166 A US 5655516 A US 5755218 A US 5813397 A	04-03-1997 12-09-1995 11-04-1995 15-08-1994 29-11-1995 08-10-1996 04-08-1994 15-01-2000 26-03-1996 17-02-2000 21-06-2000 03-03-1993 16-03-2000 24-06-1997 28-05-1997 07-03-1995 28-11-1995 28-02-1995 17-09-1992 04-06-1996 06-08-1996 22-04-1997 12-03-1996 28-05-1996 12-08-1997 26-05-1998 29-09-1998

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. onal Application No

PCT/EP 00/01443

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5743252 A		US 5826570 A	27-10-1998
US 5520166 A	28-05-1996	US 5497764 A	12-03-1996
		US 5404871 A	11-04-1995
		AT 188617 T	15-01-2000
		CA 2082168 C	26-03-1996
		DE 69230546 D	17-02-2000
		DE 69230546 T	21-06-2000
		EP 0529053 A	03-03-1993
		ES 2141104 T	16-03-2000
		JP 9164205 A	24-06-1997
		JP 2613347 B	28-05-1997
		US 5394866 A	07-03-1995
		US 5469750 A	28-11-1995
		US 5450336 A	12-09-1995
		US 5392768 A	28-02-1995
		WO 9215353 A	17-09-1992
		US 5522378 A	04-06-1996
		US 5542410 A	06-08-1996
		US 5622162 A	22-04-1997
		US 5608647 A	04-03-1997
		US 5655516 A	12-08-1997
		US 5743252 A	28-04-1998
		US 5755218 A	26-05-1998
		US 5813397 A	29-09-1998
		US 5826570 A	27-10-1998
US 5608647 A	04-03-1997	US 5450336 A	12-09-1995
		US 5404871 A	11-04-1995
		US 5743252 A	28-04-1998
		AU 6130594 A	15-08-1994
		EP 0683890 A	29-11-1995
		JP 8509545 T	08-10-1996
		WO 9417370 A	04-08-1994
		AT 188617 T	15-01-2000
		CA 2082168 C	26-03-1996
		DE 69230546 D	17-02-2000
		DE 69230546 T	21-06-2000
		EP 0529053 A	03-03-1993
		ES 2141104 T	16-03-2000
		JP 9164205 A	24-06-1997
		JP 2613347 B	28-05-1997
		US 5394866 A	07-03-1995
		US 5469750 A	28-11-1995
		US 5392768 A	28-02-1995
		WO 9215353 A	17-09-1992
		US 5522378 A	04-06-1996
		US 5542410 A	06-08-1996
		US 5622162 A	22-04-1997
		US 5497764 A	12-03-1996
		US 5520166 A	28-05-1996
		US 5655516 A	12-08-1997
		US 5755218 A	26-05-1998
		US 5813397 A	29-09-1998
		US 5826570 A	27-10-1998
US 5469750 A	28-11-1995	US 5404871 A	11-04-1995
		AU 6168194 A	15-08-1994

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 00/01443

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5469750 A		WO 9417369 A	04-08-1994
		AT 188617 T	15-01-2000
		CA 2082168 C	26-03-1996
		DE 69230546 D	17-02-2000
		DE 69230546 T	21-06-2000
		EP 0529053 A	03-03-1993
		ES 2141104 T	16-03-2000
		JP 9164205 A	24-06-1997
		JP 2613347 B	28-05-1997
		US 5394866 A	07-03-1995
		US 5450336 A	12-09-1995
		US 5392768 A	28-02-1995
		WO 9215353 A	17-09-1992
		US 5522378 A	04-06-1996
		US 5542410 A	06-08-1996
		US 5622162 A	22-04-1997
		US 5497764 A	12-03-1996
		US 5520166 A	28-05-1996
		US 5608647 A	04-03-1997
		US 5655516 A	12-08-1997
		US 5743252 A	28-04-1998
		US 5755218 A	26-05-1998
		US 5813397 A	29-09-1998
		US 5826570 A	27-10-1998

WO 9904841 A	04-02-1999	AU 8592898 A	16-02-1999
		EP 0998318 A	10-05-2000

US 5842467 A	01-12-1998	NONE	

US 3695263 A	03-10-1972	CA 929067 A	26-06-1973
		DE 2003538 A	27-08-1970
		FR 2029721 A	23-10-1970
		GB 1248302 A	29-09-1971
		JP 49011834 B	19-03-1974
		NL 7001028 A	03-08-1970
		SE 375238 B	14-04-1975
		ZA 7000541 A	25-08-1971

US 4176663 A	04-12-1979	DE 2745336 A	19-04-1979
		GB 1592548 A	08-07-1981
		CA 1097557 A	17-03-1981
		FR 2366833 A	05-05-1978
		JP 53059293 A	27-05-1978
